IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

DEAN et al.

Application No.: 09/856,927

Filed: September 19, 2001

For: A NOVEL ATP-BINDING CASSETTE PROTEIN RESPONSIBLE FOR CYTOTOXIN RESISTANCE

Customer No.: 20350

Confirmation No. 6490

Examiner: HUFF, Sheela J.

Technology Center/Art Unit: 1642

Declaration of Michael C. Dean pursuant to 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael C. Dean, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. §1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I received a Ph.D. degree in the field of Biochemistry from Boston University School of Medicine in 1984. I am currently Sr. Scientist and Chief of the Human Genetics Section, Laboratory of Genomic Diversity, National Cancer Institute, NCI-FCRDC, Frederick, MD. I have been at this and related positions since 1991. My resume is attached as Exhibit A.

3. The above-referenced patent application describes the nucleic acid (SEQ ID NO:1) encoding a new transporter protein, a ATP-binding cassette (ABC) protein MXR1, that mediates multiple drug resistance in cells. Also provided is the amino acid sequence of this protein (SEQ ID NO:2).

4. I am a named inventor on the above-identified patent application. I have read and am familiar with the contents of the application. I have also read the Office Action mailed on July 21, 2004, received in this case. I understand that the Examiner has maintained the anticipation rejection based on the Doyle reference and the Ross reference. It is my further understanding that although the Examiner has accepted that the present inventors had in their possession the MXR1 nucleic acid of SEQ ID NO:1 and the MXR1 polypeptide of SEQ ID NO:2 before the earliest effective date of the two references; yet the Examiner does not accept that the two references are antedated, because the amino acid sequences disclosed in these references are 99.8% and 99.4%, but not 100%, identical to SEQ ID NO:2 of the present application. Apparently, the Examiner takes the position that possession of SEQ ID NO:1 and SEQ ID NO:2 would not reasonably convince one of skill in the art that the inventors had possession of a genus of polynucleotide and amino acid sequences, which encompass the sequences described by Doyle and Ross.

5. This declaration is provided to demonstrate that, at the time when SEQ ID NO:1 and SEQ ID NO:2 were first obtained, the existence of naturally occurring homologues or variants of ABC proteins was known among those of skill in the art and generating man-made variants was not only contemplated but also feasible using techniques routine employed at that time.

6. At the time the present inventors obtained the nucleotide sequence and amino acid sequence of ABC protein MXR1, it was already known among those of ordinary skill in the art that there exists a family of human genes encoding a large number of ABC proteins, which share common structural features, such as ATP-binding and transmembrane segments. In fact, the well conserved sequences within these domains were used for cloning new ABC genes or for identification of novel ABC genes from human cDNA databases. *See, e.g.*, Allikmets *et al.*, *Hum. Mol. Genet.* 1996, 5(10):1649-1655, reference AC in the IDS submitted July 11, 2003. Thus, artisans in this field of research had already recognized that certain level of sequence variation can exist among ABC proteins without loss of functions.

7. In addition, at the time the present inventors first cloned the coding sequence for MXR1, a variety of suitable techniques (*e.g.*, point-directed mutagenesis) had

already been well established and widely in use for creating man-made variants of virtually any given protein. Functional assays were also available for verifying the biological activity of an ABC protein. The identification of the coding sequence for a new ABC protein, such as MXR1 of the present invention, combined with the known structural and functional characteristics of the ABC protein family, would therefore allow one with ordinary skill in the art to readily generate numerous variants of this protein without altering the protein's functionality.

8. In light of the foregoing, it is my opinion that, at the time the inventors of this application first took possession of the polynucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO:2, the general knowledge of the ABC gene family possessed by artisans in the field and the overall level of technical sophistication in the art of molecular biology would reasonably convince an ordinarily skilled artisan that the present inventors had in their possession a genus of ABC nucleic acids and polypeptides, which encompasses the species described by Doyle and Ross.

Dated: 11/17/04

By: _____
Michael C. Dean, Ph.D.

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachment (Exhibit A: Dr. Dean's resume)
60330495 V1

Principal Investigator/Program Director (Last, first, middle):

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format on next page for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Michael C. Dean, Ph.D	Chief, Human Genetics Section

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Boston University, Boston, MA	B.A.	1979	Chemistry
Boston University, Boston, MA	Ph.D.	1984	Biochemistry
Molecular Mechanisms of Carcinogenesis Laboratory, LBI-Basic Research Program, NCI-Frederick Cancer Res. Fac., Frederick, MD	Postdoctoral	1983-86	Molecular Carcinogenesis

A. Positions and Honors.

Positions and Employment

1986-1991: Scientist I, Human Genetics Analysis Laboratory, Biochemical Carcinogenesis and Development Program, Program Resources, Inc., NCI-FCRF, Frederick, Maryland.

1991-1993: Research Chemist, Human Genetics Section, Laboratory of Viral Carcinogenesis, National Cancer Institute, NCI-FCRDC, Frederick, MD.

1993-date: Sr. Scientist, Chief, Human Genetics Section, Laboratory of Genomic Diversity, National Cancer Institute, NCI-FCRDC, Frederick, MD.

Honors, Awards

1998 Cornelius P. Rhoads Memorial Award

1998 NIH Directors Award

B. Selected publications.

Campisi, J., Gray, H.E., Pardee, A.B., Dean, M., and Sonenshein, G.E.: Cell-cycle control of c-myc but not c-ras expression is lost following chemical transformation. Cell 36: 241-247, 1984.

White, R., Woodward, S., Leppert, M., O'Connell, P., Hoff, M., Herbst, J., Lalouel, J.-M., Dean, M., and Vande Woude, G.F.: A closely linked genetic marker for cystic fibrosis. Nature 318: 382-384, 1985.

Rommens, J.M., Iannuzzi, M.C., Kerem, B.S., Drumm, M.L., Melmer, G., Dean, M., Rozmahel, R., Cole L.J., Kennedy, D., Hidaka, N., Zsiga, M., Buchwald, M., Riordan, J.R., Tsui, L.C., and Collins, F.S.: Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 245: 1059-1065, 1989

White, M.B., Amos, J., Hsu, J.M., Gerrard, B., Finn, P., and Dean, M.: A frameshift mutation in the cystic fibrosis gene. Nature 344: 665-667, 1990

Dean, M., White, M.B., Amos, J., Gerrard, B., Stewart, C., Khaw, K.-T., and Leppert, M.: Multiple mutations in highly conserved residues are found in mildly affected cystic fibrosis patients. Cell 61: 863-870, 1990

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Latif, F., Tory, K., Gnarra, J., Yao, M., Duh, F.-M., Orcot, M.L., Stackhouse, T., Kuzmin, I., Modi, W., Geil, L., Schmidt, L., Zhou, F., Li, H., Wei, M. H., Chan, F., Glenn, G., Choyke, P., Walther, M. M., Weng, Y., Duan, D.-S., Dean, M., Glavac, D., Richards, F. M., Crossey, P. A., Ferguson-Smith, M. A., Le Pasilier, D., Chumakov, I., Cohen, D., Chinault, C. A., Maher, E. R., Linehan, W. M., Zbar, B., Lerman, M.: Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 260:1317-1320, 1993

Hahn, H., Wicking, C., Zaphiropoulos, P.G., Gailani, M.R., Shanley, S., Chidambaram, A., Vorechovsky, I., Holmberg, E., Unden, A.B., Gillies, S., Negus, S., Smyth, I., Pressman, C., Leffell, D.J., Gerrard, B., Goldstein, A., Dean, M., Toftgard, R., Chenevix-Trench, G., Wainwright B., Bale, A.: Mutations of the human homologue of Drosophila *patched* in the nevoid basal cell carcinoma syndrome. Cell 80:841-851, 1996

Dean, M., Carrington, M., Winkler, C., Huttley, G.A., Smith, M. W., Allikmets, R., Vlahov, D., Goedert, J., Vittinghoff, E., Buchbinder, S., Kaslow, R., Gomperts, E., and Stephen J. O'Brien: Genetic Restriction of HIV-1 Infection and Progression to AIDS by a Deletion Allele of the CKR5 Structural Gene. Science 273:1856-1863, 1996

Allikmets, R., Singh, N., Sun, H., Shroyer, N.F., Hutchinson, A., Chidambaram, A., Gerrard, B., Baird, L., Stauffer, D., Peiffer, A., Rattner, A., Smallwood, P., Li, Y., Anderson, K.L., Lewis, R.A., Nathans, J., Leppert, M., Dean M., Lupski, J.R.: A photoreceptor cell-specific ATP-binding transporter gene (*ABCR*) is mutated in recessive Stargardt macular dystrophy. Nature Genetics 15:236-246, 1997

Allikmets, R., Shroyer, N. F., Singh, N., Seddon, J.M., Lewis, R.A., Bernstein, P., Peiffer, A., Zabriskie, N., Li, Y., Hutchinson, A., Dean, M., Lupski, J.R., Leppert, M.: Mutation of the Stargardt Disease Gene (*ABCR*) in Age-Related Macular Degeneration. Science 277:1805-1807, 1997

Smith, M. W., Dean, M., Carrington, M., Winkler, C., Huttley, G.A., Lomb, D.A., Goedert, J.J., O=Brien, T.R., Jacobson, L.P., Kaslow, R., Buchbinder, S., Vittinghoff, E., Vlahov, D., Hoots, K., Hilgartner, M.W., Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, San Francisco City Cohort, ALIVE Study, and Stephen J. O'Brien: Contrasting Genetic Influence of *CCR2* and *CCR5* Variants on HIV-1 Infection and Disease Progression. Science 277: 959-965, 1997

Allikmets, R, Schriml, L.M. Hutchinson, A., Romano-Spica, V., and Dean, M.: A human placenta-specific ATP-binding cassette gene (*ABCP*) on chromosome 4q22 that is involved in multidrug resistance. Cancer Res. 58: 5337-5339, 1998

Martin, M.P., Dean, M., Smith, M.W., Winkler, C., Gerrard, B., Michael, N.L., Lee, B., Doms, R.W., Margolick, J., Buchbinder, S., Goedert, J.J., O'Brien, T.R., Hilgartner, M.W., Hoots, K., Vlahov, D., O'Brien, S.J. and Carrington, M.: Genetic acceleration of AIDS progression by a promoter variant of *CCR5*. Science 282: 1907-1911, 1998

Dean, M.: Cancer as a complex developmental disorder-Nineteenth Cornelius P. Rhoads Memorial Award Lecture. Cancer Res. 58: 5633-5636, 1998

Dean, M., Jacobson, L.P., McFarlane, G., Margolick, J.B., Jenkins, F.J., Multicenter AIDS Cohort Study, Howard, O.M.Z., Dong, H.-F., Oppenheim, J.J., O'Brien, S.J. and Carrington, M.: Reduced risk of AIDS lymphoma in individuals heterozygous for the CCR5-D32 mutation. Cancer Res., 1999.

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Miyake, K., Mickley, L., Litman, T., Zhan, Z., Robey, R., Cristensen, B., Brangi, F., Greenberger, L., Dean, M., Fojo, T., and Bates, S.: Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells: Demonstration of homology to ABC transport genes. Cancer Res. 59: 8-13, 1999.

Tucker M, Goldstein A, Dean M, Knudson A. National Cancer Institute workshop report: the phakomatoses revisited. J Natl Cancer Inst.92:530-3, 2000.

Lee, M.H., Lu, K., Hazard, S., Yu, H, Shulenin, S., Hidaka, H., Kojima, H., Allikmets, R., Sakuma, N., Pegoraro, R., Srivastava, A.K., Salen, G., Dean, M., and Patel, S.B.: Identification of a gene, *ABCG5*, important in the regulation of dietary cholesterol. Nat. Genet. 27:79-83, 2001.

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Honjo, Y., Hrycyna, C.A., Yan Q.W., Medina-Perez, W.Y., Robey, R.W., van de Laar, A., Litman, T., Dean, M., and Bates, S.E: Acquired mutations in the *MXR/BCRP/ABCP* gene alter substrate specificity in *MXR/BCRP/ABCP*-overexpressing cells. Cancer Research 61:6635-6639, 2001.

Dean, M., Rzhetsky, A., and Allikmets, R.: The human ATP-binding cassette (ABC) transporter superfamily. Genome Research. 11:1156-1166, 2001.

Dean, M., Carrington, M., and O'Brien, S.J.: Balanced polymorphism selected by genetic versus infectious human disease. Ann. Rev. Hum. Genet. 3:263-92, 2002.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Gold, B., Goldman, D., Dean, M., Lu, B., and Weinberger, D.R.: BDNF Val66Met polymorphism affects vesicular packaging and human hippocampal function. Cell 112:257-269, 2003.

Shulenin, S., Nogee, L.M., Annilo, T., Wert, S.E., Whitsett, J.A., and Dean, M. The ABCA3 gene is frequently mutated in human newborns with fatal surfactant deficiency. N.Eng.J.Med. 350:1296-1303, 2004.

C. Research Support

Ongoing Research Support

ZO1 BC 05652-09 LGD — 10/91 - ongoing — 50%
NIH — $322,064
Identification of Single Nucleotide Polymorphisms in Cancer-Related Genes
Principal Investigator: Michael Dean

The major goals of this project are to identify common variants in genes likely to play a role in cancer and to type these variants in cancer cohorts.

ZO1 BC 05725-07 LGD — 10/93 - ongoing — 50%
NIH — $393,190
ABC Transporters in Human Disease and Drug Resistance
Principal Investigator: Michael Dean

The major goals of this project are to characterize genes from the human and mouse ABC family and study their role in disease and drug resistance.